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(54) **Title:** PHARMACEUTICAL PREPARATION COMPRISING EICOSAPENTAENOIC ACID AND/OR STEARIDONIC ACID

(57) **Abstract**

A pharmaceutical preparation for the treatment of schizophrenia and/or tardive dyskinesia using an oil comprising eicosapentaenoic acid (EPA) and/or stearidonic acid (SA) in amounts of more than 20 %, preferably more than 40 % and very preferably more than 70 % by weight of the total (preferably of the total unsaturated) fatty acids present.

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PHARMACEUTICAL PREPARATION COMPRISING EICOSAPENTAENOIC ACID AND/OR STEARIDONIC ACID

FIELD OF THE INVENTION

The invention relates to fatty acid treatment in schizophrenia.

Background

The essential fatty acids and their conversions in the body are shown in the following table.

n-6 EFAs		n-3 EFAs
18:2n-6 Linoleic acid (LA)		18:3n-3 α-linolenic acid (ALA)
↓	δ-6-desaturase	↓
18:3n-6 γ-Linolenic acid (GLA)		18:4n-3 Stearidonic acid, (SA)
↓	elongation	↓
20:3n-6 Dihomo-γ-linolenic acid (DGLA)		20:4n-3 Eicosatetraenoic acid
↓	δ-5-desaturase	↓
20:4n-6 Arachidonic acid (AA)		20: 5n-3 Eicosapentaenoic acid (EPA)
↓	elongation	↓
22:4n-6 Adrenic acid (AdrA)		22:5n-3
↓	δ-4-desaturase	↓
22:5n-6		22-6n-3 Docosahexaenoic acid (DHA)

The acids, which in nature are of the all - cis configuration, are systematically named as derivatives of the corresponding octadecanoic, eicosanoic or docosanoic acids, e.g.LA z,z-octadeca - 9,12 - dienoic acid or DHA z,z,z,z,z,z - docosa- 4,7,10,13,16,19 - hexaenoic acid, but numerical designations based on the number of carbon atoms, the number of centres of unsaturation and the number of carbon atoms from the end of the chain to where the unsaturation begins, such as, correspondingly, 18:2 n-6 or 22:6 n-3, are convenient. Initials, e.g. EPA, and shortened forms of the name e.g. eicosapentaenoic acid, are used as trivial names in some instances.

In previous patent applications EPA-0347856 and EPA-0599576 we have drawn attention to the action of various essential fatty acids in schizophrenia and have claimed the use of these fatty acids in treatment. We have particularly drawn attention to the low red cell levels of arachidonic acid (AA) and docosahexaenoic acid (DHA) and to the use of these fatty acids.

Present Work

We have now unexpectedly found that one particular essential fatty acid which was previously accorded only a minor role is in fact particularly effective in treatment. This is eicosapentaenoic acid (EPA; 20:5n-3) which is present in the brain in only small amounts compared to AA and DHA. However, in a trial of treatment we have found that EPA is exceptionally effective in treatment of schizophrenia. Particularly effective are preparations comprising EPA in amounts of more than 20% of the total fatty acids present (preferably the total unsaturated fatty acids present), preferably more than 40% and very preferably more than 70%.

Studies of the use of omega-3 essential fatty acids in treatment, using a mixture of DHA and EPA, have previously shown modestly beneficial effects (Mellor et al, Human Psychopharmacology 11:39-46, 1996). The preparation used contained 18% of EPA and 12% of DHA and so far as this disclosure goes the therapeutic effects could have been caused by either component or both. An analysis of the relationship between fatty acid change and schizophrenia symptoms showed that a rise in the total omega-3 content of red cell membranes was associated with a fall in schizophrenic symptoms.

We therefore decided to try to determine the relative importance of EPA and DHA in schizophrenia. A study was carried out with 30 schizophrenia patients, most of whom had both positive and negative symptoms as shown by the positive and negative symptom scale (PANSS) and also had some evidence of tardive dyskinesia as shown by the abnormal involuntary movements scale (AIMS). Patients were randomly assigned on a double blind basis to treatment with 20ml of a placebo emulsion, 20ml of a 40% emulsion providing 8g of oil containing approximately 2.0g of EPA and 0.4g of DHA per day ('EPA group'), and 20ml of an emulsion providing approximately 2.3g of DHA and 0.5g of EPA per day ('DHA group') in 8g of oil. Patients were scored at baseline and at the end of 12 weeks of treatment. In the placebo group, 9 patients were unchanged or deteriorated on the PANSS and AIMS scores and one improved. In the DHA group, seven patients were unchanged or deteriorated and three patients improved. In contrast, in the EPA group one patient was unchanged but nine patients showed improvement. The improvement was seen in both the negative and positive symptom scores and in the AIMS score. There was therefore a broad spectrum improvement in all aspects of the schizophrenia syndrome. The DHA group was not significantly different from placebo whereas the EPA group was significantly better than both the DHA group and the placebo group ($p < 0.02$ in both cases).

It is therefore possible to conclude that the main therapeutic effect of treatment with EFAs is attributable to the effect of EPA. The other EFAs may contribute to some degree but there can be no doubt that EPA is primarily responsible for the positive effects of treatment with omega-3 EFA preparations. We concluded that EPA should also be effective in other psychiatric disorders such as Alzheimer's disease and depression since low levels of n-3 fatty acids have been shown in the blood and/or the brain of patients with these disorders also. Two patients with severe depression not responsive to the usual anti-depressants were therefore treated with the EPA formulation as used in the schizophrenia trial. Within 4 weeks both had shown remarkable improvement in their symptoms.

While we cannot be certain of the mechanism by which EPA is working, one possibility is that it is inhibiting the enzyme, phospholipase A2. There is considerable evidence that phospholipase (PL) A2 activity is elevated in schizophrenia (Horrobin et al, Schizophrenia Research 1994; 13: 195-207). Compounds which safely inhibit PLA2 might therefore be expected to have a therapeutic effect. In in vitro studies of the effects of fatty acids on PLA2 activity we have found that EPA is a potent inhibitor, whereas the relatively similar fatty acid, DHA is not. This might explain why DHA did not prove effective in the clinical studies.

We have further found that another n-3 fatty acid, stearidonic acid (18:4 n-3), is as effective in inhibiting PLA2 as is EPA. EPA and SA are 20- and 18- carbon fatty acids which have in fact been shown to inhibit the activity of phospholipase A_2 (Finnen, Biochem Soc. Trans 1991; 19:915). In contrast, DHA is A 22-carbon fatty acid which like other 22-carbon acids does not inhibit phospholipase. This may offer an explanation for the differences between EPA and DHA since there is evidence for overactivity of phospholipase A_2 in schizophrenia. We therefore propose that stearidonic acid will be effective in treating schizophrenia and the other disorders and we include its use for that purpose alone or with EPA.

The n-6 EFAs such as linoleic acid, gammalinolenic acid (GLA) dihomogammalinolenic acid (DGLA) and arachidonic acid (AA) are important in brain structure. GLA can be metabolised to DGLA and AA. We therefore tried to see whether the addition of an oil containing linoleic acid and GLA would be beneficial in two individuals who had responded to EPA. In fact their condition appeared to be less good with addition of the n-6 EFAs. It is therefore better to treat with EPA preparations in which the levels of n-6 EFAs are kept at a low level compared to the concentration of EPA. Either n-6 EFAs should be absent or if present at a ratio to EPA of not more than 1:3, preferably 1:4 or less.

In any case to ensure that the effects secured are not countered the weight ratio of SA/EPA to any DHA present is desirably not less than 3:1 by weight and desirably 4:1 or more.

Statement of Invention

The invention is set out in the claims herein but inter alia provides a pharmaceutical preparation for the treatment of schizophrenia and/or tardive dyskinesia using an oil comprising eicosapentaenoic acid (EPA) and/or stearidonic acid (SA) in amounts of more than 20%, preferably more than 40% and very preferably more than 70% by weight of the total (preferably of the total unsaturated) fatty acids present. Corresponding methods of treatment, and methods of preparation of medicaments, wherein such oils as used, are also within the invention, as are corresponding treatments of depression or Alzheimer's disease or other dementias.

The EPA can be provided in any appropriate way which will elevate the levels of EPA in the blood. Mono-, di-, and tri-glycerides, mono- or di-esters, salts, cholesterol esters, amides, phospholipids, free acids or any other appropriate form may be used to deliver the

EPA. Mono or diesters of EPA as specified in previous applications where the present inventor is a co-inventor (PCT/GB96/01052 and 01053), published respectively as WO96/34855 and WO96/34846 are particularly convenient forms in which the EPA may be administered. The EPA may be derived from fish or marine mammal oils, microbial oils or even from total chemical synthesis. The EPA dose used may range from 10mg to 100g/day, preferably 100mg to 20g/day and very preferably from 500mg to 10g/day. Oral, enteral, parenteral, topical, or any other appropriate route of administration may be used. Stearidonic acid may be provided in similar doses and in similar ways, alone or with the EPA

Examples

The study described above illustrates treatment according to the invention but examples of suitable formulations are as follows:-

1. Soft gelatine capsules, each containing 200mg of EPA in the form of one of the following:
   a) An oil containing 22% EPA derived from marine or microbial sources.
   b) An oil containing 56% EPA derived from marine or microbial sources.
   c) An oil containing 75% of EPA derived from marine or microbial sources.
   d) An oil containing 95% of EPA derived from marine, microbial or synthetic sources.
   e) EPA 1-3 propane diol diester.

2. Oils as in examples la to 1e but formulated as an emulsion for oral administration. The emulsion may contain 5 to 50% of the oil emulsified with emulsifying agents known to these skilled in the art including natural, synthetic and semi-synthetic agents such as phospholipids and galactolipids, the latter for example as described in PCT SE95/00115 published as WO95/20943.

3. Emulsions as in 2 but sterilised and appropriately formulated for intravenous administration.

4. Oils as in examples la to 1e, sterilised and formulated for intramuscular or sub-cutaneous injection.

5. Oils as in examples la to 1e formulated for topical administration using patch or other technologies known to those skilled in the art.

6-10. As Examples 1-5 except that stearidonic acid is used instead of EPA or in admixture with it e.g. half and half.

CLAIMS

1. A pharmaceutical preparation for the treatment of schizophrenia and/or tardive dyskinesia, using an oil comprising eicosapentaenoic acid (EPA) and/or stearidonic acid (SA) in amounts of more than 20%, preferably more than 40% and very preferably more than 70% by weight of the total (preferably of the total unsaturated) fatty acids present.

2. A method of treating, or a method of preparation of a medicament for treating, schizophrenia and/or tardive dyskinesia whereby EPA and/or SA is provided in the form of an oil containing more than 20% of said acid(s), preferably more than 40% and very preferably more than 70% by weight of the total (preferably total unsaturated) fatty acids present.

3. A pharmaceutical preparation according to claim 1, or method according to claim 2, wherein the weight ratio of SA/EPA to any DHA present is not less than 3:1 and is preferably 4:1 or more.

4. A pharmaceutical preparation according to claim 1 or 3 or method according to claim 2 or 3 wherein the weight ratio of SA/EPA to n-6 EFAs is present is not less than 3:1 and is preferably 4:1 or more, or n-6 EFAs are absent.

5. A pharmaceutical preparation according to claim 1, 3 or 4 or method according to claim 2 , 3 or 4 but for the treatment of depression .

6. A pharmaceutical preparation according to claim 1, 3 or 4 or method according to claim 2, 3 or 4 but for the treatment of Alzheimer's disease or other dementias.

7. Pharmaceutical preparation or medicament prepared as above which is suited to, or a method of treatment as above which employs, administration of 10mg to 100g, preferably 100mg to 20g, very preferably 500mg to 10g, EPA and/or SA daily.

8. Use of EPA and/or SA in the preparation of a medicament for the treatment of schizophrenia and/or tardive dyskinesia, or depression, or Alzheimer's disease or other dementias, in the form set out in claim 1, for the administration of 10mg to 100g, preferably 100mg to 20g, very preferably 500 mg to 10g, EPA and/or SA daily, desirably with the SA/EPA to DHA ratio set out in claim 3, and the weight ratio of SA/EPA to n-6 EFAs if present set out in claim 4; and such treatment itself.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/02738

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/20 //(A61K31/20,31:20)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 347 056 A (EFAMOL HOLDINGS) 20 December 1989 see page 5, line 28-29 see page 7, line 29-30 see page 7, line 29-30 ---	1,2,5-8
X	EP 0 454 102 A (EFAMOL HOLDINGS PLC) 30 October 1991 see page 6, line 6-7 see page 7, line 44-45; claims 1-8 ---	1,2,5-8
X	GB 2 229 363 A (TISDALE MICHAEL JOHN ;BECK SUSAN ANNE (GB); CANCER RES CAMPAIGN TE) 26 September 1990 see abstract; claims 9-12 -----	1,3-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
27 January 1998	06. 02. 98

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 97/02738

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 2-8 (partly)

because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Remark : Although claims
are directed to a method of treatment of the
human/animal body , the search has been carried out and based on the
alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/02738

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0347056 A	20-12-89	AU 618814 B	09-01-92
		AU 3597489 A	14-12-89
		AU 633442 B	28-01-93
		CA 1334004 A	17-01-95
		EP 0454102 A	30-10-91
		ES 2053990 T	01-08-94
		IE 63303 B	05-04-95
		JP 2032017 A	01-02-90
		NZ 239126 A	27-07-97
		US 4977187 A	11-12-90
		US 5120760 A	09-06-92
EP 0454102 A	30-10-91	AU 618814 B	09-01-92
		AU 3597489 A	14-12-89
		AU 633442 B	28-01-93
		CA 1334004 A	17-01-95
		EP 0347056 A	20-12-89
		ES 2053990 T	01-08-94
		IE 63303 B	05-04-95
		JP 2032017 A	01-02-90
		NZ 239126 A	27-07-97
		US 4977187 A	11-12-90
		US 5120760 A	09-06-92
GB 2229363 A	26-09-90	AT 155037 T	15-07-97
		AU 643201 B	11-11-93
		AU 5331090 A	22-10-90
		DE 69031033 D	14-08-97
		DE 69031033 T	20-11-97
		EP 0464084 A	08-01-92
		WO 9011073 A	04-10-90
		HK 2894 A	21-01-94
		JP 5504936 T	29-07-93
		SG 137193 A	31-03-94
		US 5457130 A	10-10-95